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(56) Documents cited
None

(58) Field of search
C2C

(54) Benzoic acid derivatives

(57) The dicarboxylic, heterocyclic and substituted benzoic acid alkylene bridged piperidyl amides and esters are serotonin M antagonists.

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SPECIFICATION

Benzoic acid derivatives

5 This invention relates to benzoic acid derivatives.

It has been proposed (see for example J.R. Fozard in Advances in Neurology Vol. 33 Raven Press New York 1982) to use compounds with serotonin antagonistic effects, i.e. 5HT blocking effects in the treatment of migraine. Particularly interesting are the compounds which antagonise the M-receptors. A particularly active compound of this type is Metoclopramide (US Patent 3177252) which J.B. Hughes in Med.J. Australia 2 No.

10 17, p. 580 (1977) has reported to lead to an immediate effect on a migraine attack on slow i.v. injection of 10 mg.

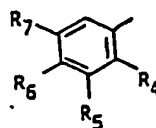
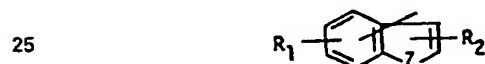
Subsequently further compounds with serotonin-M antagonistic effect has been described. European Publication 67770 describes a narrow class of tropane phenyl esters.

The present invention provides a new group of compounds which has not been specifically suggested 15 before in the literature and which have particularly interesting pharmacological properties, for example serotonin M antagonistic activity and anti-arrhythmic agents, e.g. as indicated by potency in the vagus nerve test mentioned hereinafter.

The present invention provides in one aspect compounds of formula I

20 A-B-C-D- I 20

wherein A is a group of formula

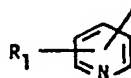


30 (a)

(b)



oder



40 (c)

(d)

wherein the free valence is attached to either fused ring in formula (a) or (c),

X-Y is -CH=CH-, -O-CH2- or -N=CH-,

45 Z is CH2, -NR3-, -O-, or -S-,

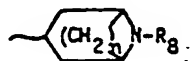
R1 and R2 are independently hydrogen, halogen, (C1-4)-alkyl, (C1-4) alkoxy, hydroxy, amino, (C1-4) alkylamino, di (C1-4) alkylamino, mercapto or (C1-4) alkylthio, R3 is hydrogen (C1-4) alkyl, (C3-5) alkenyl, aryl or arylalkyl,

R4 to R7 are independently hydrogen, amino, nitro, (C1-4) alkylamino, di(C1-4) alkylamino, halogen, 50 (C1-4)-alkoxy, (C1-4)alkyl, (C1-4) alkanoylamino, pyrrolyl, sulfamoyl, or carbamoyl

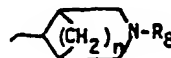
B is -CO- or -SO2-

C is -O- or -NH-

55 D is a group of formula



(e)



(f)



(g)

oder



(h)

15 wherein

R_8 is hydrogen, (C_{1-7}) alkyl, (C_{3-5}) alkenyl or aralkyl and n is 2,3 or 4 with the provisos that

- 1) when A is a group of formula (a) and B is $-\text{CO}-$, then D is other than a group of formula (e) or (g),
- 2) when A is a group of formula (b) wherein R_4 to R_7 are each hydrogen, B is $-\text{CO}-$ and C is $-\text{O}-$, then D is other than a group of formula (f) or (h) wherein R_8 is methyl,
- 3) when A is a group of formula (d) wherein R_1 is hydrogen or alkoxy and B is $-\text{CO}-$ then D is other than a group of formula (e) wherein n is 2,
- 4) when A is a group of formula (d) wherein R_1 is hydrogen, B is CO and C is $-\text{O}-$ then D is other than a group of formula (g)
- 5) when A is a group of formula (b), B is $-\text{CO}-$ and D is (e) or (g) then at least one of R_4 to R_7 in the formula (b) is sulfamoyl or carbamoyl, their acid addition salt and quaternary ammonium salts, hereinafter referred to as compounds of the invention.

Any alkyl moiety preferably is methyl, ethyl or propyl. Alkoxy is preferably methoxy or ethoxy. Aralkyl is conveniently aryl (C_{1-4}) alkyl. Alkenyl is preferably allyl or methallyl. Any aryl moiety is preferably unsubstituted phenyl or phenyl mono- or poly-substituted by (C_{1-4}) alkyl, e.g. methyl, halogen, e.g. fluorine, hydroxy, or (C_{1-4}) alkoxy, e.g. methoxy. Preferably any substituted aryl group is mono-substituted. Aralkyl is conveniently benzyl. Halogen is fluorine, chlorine, bromine or iodine.

A is conveniently a group of formula (a). In the group of formula (a), the group $-\text{B}-$ may be attached to the ring carbon atom in position 2,3,4,5,6 or 7 of the nucleus, but preferably in position 4 and 5. Most preferably the $-\text{B}-$ group is attached to the ring containing Z, especially in position 3. Preferably A is indole.

R_1 is attached to the ring carbon atom in position 4,5,6 or 7 of the nucleus, preferably position 5 and R_2 is attached to the ring carbon atom in position 2 or 3 of the nucleus. Tautomers are also covered by formula I e.g. when R_2 is hydroxy or mercapto in the 2 position. R_3 is conveniently hydrogen or alkyl.

In a group of formula (b) preferably one of R_4 to R_7 is other than hydrogen, and/or R_4 is hydrogen, or (C_{1-4}) alkyl and/or R_5 is hydrogen or halogen or carbamoyl and/or R_6 is hydrogen or (C_{1-4}) alkyl and/or R_7 is hydrogen, halogen or sulphamoyl.

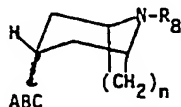
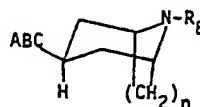
Examples of the group of formula (b) include 2-methoxy-phenyl, p-tolyl, 3-carbamoylphenyl, 3-sulphamoylphenyl, 3,5-dimethylphenyl or 3,5-dichlorophenyl.

If A is a group of formula (c) wherein X-Y is $-\text{CH}=\text{CH}-$, the free valence is preferably in position 2,3,6 or 7 of the nucleus. R_1 is preferably in position 6 or 7. R_2 is preferably in position 2 or 3. R_2 may replace one of the H atoms in X-Y.

If A is a group of formula (c) wherein X-Y is $-\text{O}-\text{CH}_2-$, or $-\text{N}=\text{CH}-$, the N or O atom is in position 1, the free valence is preferably in position 2,3,6 or 7. R_1 is preferably in position 2 or 3. R_2 may replace one hydrogen in X-Y.

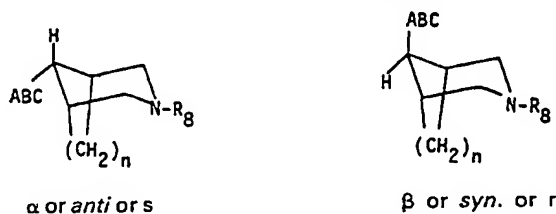
If A is a group of formula (d), then the free valence is preferably in position 3 or 4. R_1 is preferably in position 2 or 3.

The group of formula (e) may exist in two different configurations namely:-

 α - or endo- or r- β - or exo- or s-

The two different configurations may be appreciated by making the groups of formula (e) have a configuration wherein a reference plane may be drawn through the carbon atoms of the piperidyl ring and the nitrogen atom is above the plane and the alkylene bridge is below the plane. The group of formula (e) has the α configuration when the group ABC is below the plane on the same side as the alkylene bridge. This corresponds to the endo configuration and also to the configuration in tropine etc. The group of formula (e) has the β -configuration when it is above the plane on the same side as the nitrogen bridge. This corresponds to the exo configuration and also the configuration in pseudotropine etc. Used hereinafter is the exo/endo nomenclature. The endo isomers are preferred.

The group of formula (f) may exist in two different configurations:-

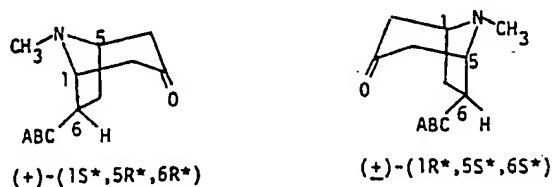


In the anti configuration the group ABC is oriented away from the nitrogen atom and in the anti configuration is oriented towards the nitrogen atom (see Chemical abstracts, Index Guide 1982 p 1701). In Org. Chem. 35 2840 and 2867 (1970) the configuration of the carbon to which the group ABC is bound is designated *r* or *s*. Hereinafter the syn/anti nomenclature is used.

The preferred configuration is anti.

A group of formula g is also known as quinuclidinyl. Conveniently this is 3- or 4-quinuclidinyl and especially 3-quinuclidinyl.

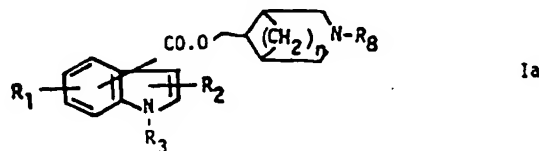
The group of formula h may exist in two configurations which are diastereoisomers:-



In the groups of formula (e), (f) and (h) R_8 is preferably allyl especially methyl.

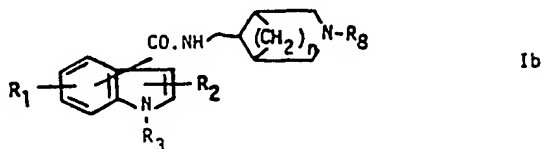
B is preferably CO
C is preferably O.

A group of compounds comprises compounds of formula Ia



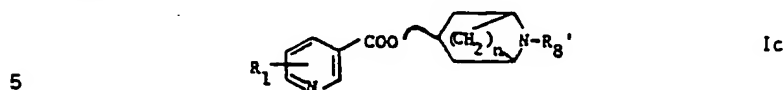
wherein the carbonyl group is attached to either fused ring, and R_1 , R_2 , R_3 , R_8 and n are as defined above, as well as acid addition salts and quaternary ammonium salts thereof.

Another group of compounds comprises compounds of formula Ib



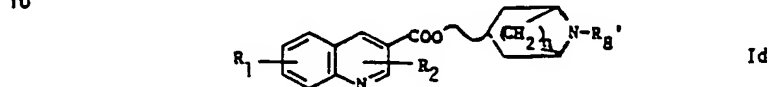
wherein the carbonyl group is attached to either fused ring, and R_1 , R_2 , R_3 , R_8 and n are as defined above, as well as acid addition salts and quaternary ammonium salts thereof.

A group of compounds comprises compounds of formula Ic



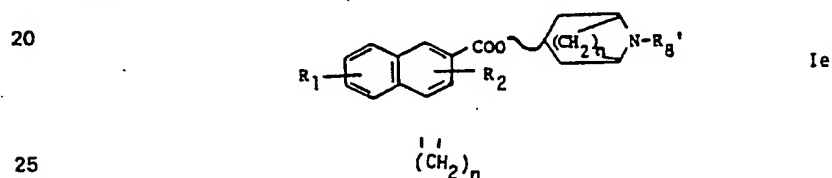
wherein R₁ and n are as defined above and R₈¹ is hydrogen or (C₁₋₄) alkyl, as well as acid addition salts and quaternary ammonium salts thereof.

10 A group of compounds comprises compounds of formula Id



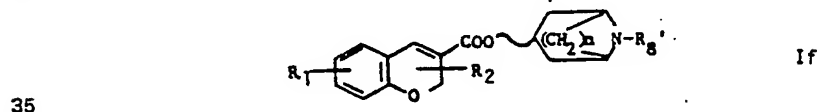
15 wherein R₁, R₂, n and R₈¹ are as defined above, as well as acid addition salts and quaternary ammonium salts thereof.

A group of compounds comprises compounds of formula Ie



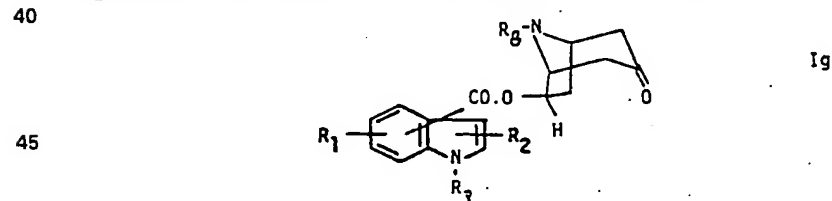
wherein R₁, R₂, n and R₈¹ are as defined above, as well as acid addition salts and quaternary ammonium salts thereof.

30 A group of compounds comprises compounds of formula If



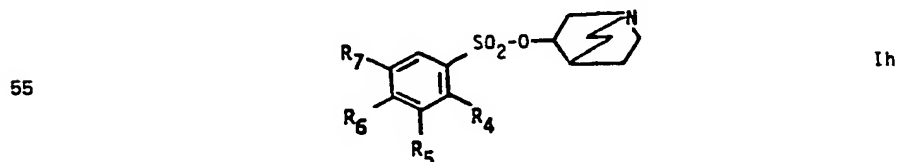
wherein R₁, R₂, n and R₈¹ are as defined above, as well as acid addition salts and quaternary ammonium salts thereof.

A group of compounds comprising compounds of formula Ig



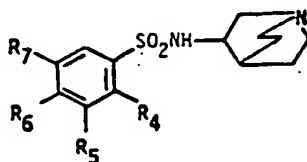
wherein the carbonyl group may be attached to either fused ring R₁, R₂, R₃, R₈ and n are as defined above, as well as acid addition salts and quaternary ammonium salts thereof.

A group of compounds comprising compounds of formula Ih



60 wherein R₄ to R₇ are as defined above, as well as acid addition salts and quaternary ammonium salts thereof.

A group of compounds comprising compounds of formula Ii



Ii

10 wherein R_4 to R_7 are as defined above,
as well as acid addition salts and quaternary ammonium salts thereof.

Another group of compounds comprises compounds of formula I wherein

15 A is a group of formula (c) or (d)
B is CO
D is a group of formula (e) or (g)

as well as acid addition salts and quaternary ammonium salts thereof.

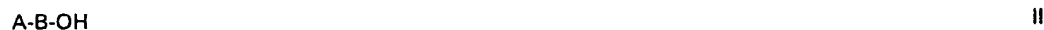
20 A further group of compounds comprises compounds of formula I wherein

A is group of formula (a), or a group of formula (b) wherein each R_4 to T_7 is other sulfamoyl or carbamoyl
B is CO
D is a group of formula (f),

25 as well as acid addition salts and quaternary ammonium salts thereof. In a further sub-group in the formula
(a) R_1 and R_2 are other than alkyl.

In the all above sub-groups of formula I compounds the provisos to formula I also apply.

30 In particular the present invention provides a process for the production for a compound of formula I as
well as acid addition salts thereof or quaternary ammonium salts thereof which includes the step of
a) condensing an appropriate compound of formula II



35 wherein A and B are as defined above, a reactive derivative thereof, or a precursor of the acid or derivative,
with an appropriate compound of formula III



40 wherein C and D are as defined above, or a precursor of the compound or,
b) alkylating a compound of formula I having a secondary amino group to produce a compound of formula I with a tertiary amino group,

c) deprotecting any protected form of a compound of formula I to obtain a compound of formula I,

45 d) halogenating a compound of formula I wherein A is a group of formula (a) and R_2 is hydrogen to obtain
the corresponding compound wherein R_2 is halogen, or

e) alkoxyating a compound of formula I wherein A is a group of formula (a) and R_2 is halogen to obtain the
corresponding compound wherein R_2 is alkoxy, and
recovering the resultant compound of formula I as such or as acid addition salt or as a quaternary
ammonium salt thereof.

50 It is assumed that in all these processes the configuration of the groups of formula (e), (f) and (h) remain
unchanged.

The condensation process of the invention to obtain amides and esters may be effected in conventional
manner for analogous compounds.

55 For example, the carboxylic acid group may be activated in the form of a reactive acid derivative,
especially for the production of amides.

Suitable reactive acid derivatives may be formed as in silin intermediates by reaction with N,N'-carbonyl-
diimidazole or with N-hydroxy-succinimide. Alternatively an acid chloride may be used, e.g. produced by
reaction with oxalyl chloride. In the case of sulphonic acids, the acid chloride is preferably used.

60 For production of esters, the alcohol may be used e.g. in the form of an alkali metal salt, preferably the
lithium salt. Such salts may be produced in conventional manner, e.g. by reaction of a n-butyl lithium with
the alcohol in tetrahydrofuran. If desired a heterocyclic or tertiary amine, e.g. pyridine or triethylamine, may
be present, especially for the production of amides.

Suitable reaction temperatures may be from about -10° to about 100° .

Other suitable inert organic solvents include, e.g. tetrahydrofuran or dimethoxyethane.

65 The compounds of the invention may be converted into other compounds of the invention, e.g. in

conventional manner. Some interconversions are exemplified in processes b), c), d) and e).

The alkylation reaction of process b) may be effected in conventional manner. Any free amino group may be alkylated, especially compounds of formula (a) wherein Z is NH. Appropriate alkylation conditions include reaction with an alkyl halide in the presence of a sodium alcoholate. Suitable temperatures may be from about -50° to about -30°C .

The deprotection reaction of process c) is specifically suitable for the production of compounds with secondary amino groups, e.g. $R_8 = \text{H}$ in the group of formulae (e), (f) and (h) or primary amino groups of formula (b), e.g. $R_8 = \text{NH}_2$.

For example a compound of formula I may be produced in protected form, e.g. R_8 being replaced by a secondary amino protecting group such as benzyl. The benzyl group may be split off in conventional manner, e.g. by hydrogenation to produce the corresponding compound of formula I wherein R_8 is hydrogen. Suitably the hydrogenation may be effected in the presence of a palladium on active charcoal at room temperature or at a slightly elevated temperature. Suitable solvents include acetic acid, ethyl acetate or ethanol.

A primary amino group as R_8 may be protected by e.g. N-benzyloxycarbonyl. This group may be split off by hydrogenation analogously to that indicated above. In the presence of a benzyl group the N-benzyloxycarbonyl group is generally split off first so that this group may be selectively split off.

Also the amino group may be in the form of a nitro group. This can be selectively reduced in conventional manner, e.g. by iron in hydrochloric acid.

Halogenation according to process d) may be effected in conventional manner. For example with N-chloro-succinimide may lead to chlorination. Such reactions may be effected in a suspension in chloroform. Reaction with N-iodo-succinimide may alternatively lead to iodination.

Replacement of reactive halogen groups according to process e) may be effected in conventional manner e.g. by reaction with a appropriate alcohol at e.g. room temperature from 10 to 20 hours at least.

A precursor of a starting material may be employed if desired. Such a precursor may be capable of being converted into the starting material in conventional manner but instead the process of the invention is carried out with the precursor and the other starting material or materials or a precursor thereof. The resultant product is converted into the compound of the invention in conventional manner, e.g. by using the same reaction conditions by which the precursor may be converted into the starting material. Typical precursors include protected forms of a starting material, e.g. wherein amino groups are temporarily protected.

The compounds of the invention may be isolated and purified in conventional manner. If isomeric mixtures starting materials containing groups of formula (e), (f), and (h) are used then the final compounds may be purified by e.g. column chromatography.

Compounds of formula III are wherein C is $-\text{NH}-$, D is a group of formula (f) are new and form part of the present invention. The compounds have never been specifically suggested before although they fall under various generic disclosures.

The compounds are useful intermediates by virtue of the functional groups present therein, e.g. the amino group, e.g. for the preparation of a wide range of pharmacologically active compounds, e.g. amides as described herein which have an interesting pharmacological profile and have never been disclosed as Serotonin M antagonists and other activities disclosed hereinafter. These compounds of formula III may for example be produced by reduction of the corresponding oxime, in analogous manner to other known compounds of formula III.

The above reduction may be effected, e.g. by catalytic hydrogenation, e.g. over platinum (believed to lead primarily to anti isomers), Bouveault-Blanc reaction procedures, e.g. sodium/amy alcohol or butanol (believed to lead primarily to isomers), or aluminium hydride procedures or sodium borohydride (also leading primarily to the anti isomers).

Any mixture of syn and anti forms may be separated by chromatography.

Compounds of formula III wherein B is $-\text{O}-$ are known and may be produced in conventional manner by reduction of the corresponding ketone.

Other compounds of formula III are in general known. Insofar as the production of an starting material is not particularly described herein, it is known, or may be produced in analogous manner to known compounds, in analogous manner to that described herein, e.g. the examples, or to known procedures for analogous compounds.

Free base forms of compounds of the invention may be converted into salt forms. For example acid addition salts may be produced in conventional manner by reacting with a suitable acid, and vice versa. Suitable acids for salt formation include hydrochloric acid, malonic acid, hydrobromic acid, maleic acid, malic acid, fumaric acid, methanesulphonic acid, oxalic acid, and tartaric acid. Quaternary ammonium salts of the compounds of the invention may be produced in conventional manner, e.g. by reaction with methyl iodide.

In the following examples all temperatures are in degrees Centigrade and are uncorrected.

The configuration of the title compounds of Examples 1 and 2 have been confirmed by x-ray analysis. The configuration of the remaining compounds is believed to follow that of the starting materials of formula III which were used pure, except where otherwise stated.

EXAMPLE 1: *Indol-3-yl carboxylic acid-9-anti-3-methyl-3-aza-bicyclo[3.3.1]non-9-yl amide*

a) *Indol-3-yl carboxylic acid chloride*

- 32.2 g (0.2 M) dry indol-3-yl carboxylic acid are suspended in 150 ml absolute methylene chloride. 26 ml oxalyl chloride are added to the stirred mixture at 20°C over 30 minutes. Gas evolution results. The mixture is stirred for 3 1/2 hours at 20°C. 150 ml Hexane are added. The mixture stirred for another 20 minutes and the resultant heading compound filtered off, washed with methylene chloride/hexane 1:1 dried at 20° in a vacuum to give beige crystals, M.pt. 135-136° (decomp) which are used further without purification.

b) *3-methyl-3-aza-bicyclo[3.3.1]nonan-9-one oxime*

- 51 g sodium acetate dihydrate and 26.5 g hydroxylamine hydrochloride are pounded in a mortar to a thin paste. 300 ml methanol are added and the mixture filtered off. The filtrate is treated with 30.6 g 3-methyl-3-azabicyclo[3.3.1]nonan-9-one and 500 ml methanol is added. The resultant suspension is stirred for 2 1/2 hours at 50°C. About half the methanol is evaporated. The residue is adjusted with potassium hydrogen carbonate solution to pH 8 and extracted with chloroform, and three times with chloroform containing 10% isopropanol. The combined organic phases are dried and concentrated to give the crystalline heading compound. M.pt. 111-112°.

c) *9-anti-3-methyl-3-aza-bicyclo[3.3.1]non-9-yl amine*

- A solution of 9.6 g (100%) sulphuric acid in 30 ml absolute tetrahydrofuran are added to a cooled and stirred mixture of 13.5 lithium aluminium hydride in 140 ml absolute tetrahydrofuran at -10° to 0° C within 45 minutes. The mixture is allowed to stand for 2 hours. A solution of 14.1 g 3-methyl-3-azabicyclo[3.3.1]nonan-9-one oxime in 130 ml absolute tetrahydrofuran is added in a thin stream over 30 hours to the stirred mixture at 20-30°C and allowed to react further at 40° for 3 hours and overnight for 15 hours (overnight) at room temperature. To work up the reaction mixture is cooled to -15 to 0°C and a mixture of 40 ml water in 40 ml tetrahydrofuran is added carefully. The mixture is allowed to react at room temperature. The mixture is filtered off. The residue is washed twice with tetrahydrofuran. The organic phases are combined, dried in a low vacuum (400 mm Hg). The residue is distilled.

- 1st Fraction (10 mm Hg and 80-88°) n = 1.4620
2nd Fraction (8mm Hg and 87-88°) n = 1.5050
3rd Fraction (8 mm Hg and 88°) n = 1.5050

(All specific refractive indexes measured at 20° and the D line)
Fractions 2 and 3 contain the heading compound.

d) *Indol-3-yl carboxylic acid-9-anti-3-methyl-3-azabicyclo[3.3.1]-non-9-yl amide*

- 5 ml pyridine and then a solution of 5.5 g 9-anti-3-methyl-3-aza-bicyclo[3.3.1]non-9-yl amine in 25 ml absolute methylene chloride are added dropwise to a stirred suspension of 5.4 g indol-3-yl carboxylic acid chloride (produced in step a) in 25 ml absolute methylene chloride at -15° to -5°C. The resultant mixture is stirred at room temperature for 20 hours, and partitioned between methylene chloride and 1N.2N aqueous sodium carbonate. The organic phases are combined, concentrated and the resultant precipitate filtered off. The filtrate is concentrated further to give a bright yellow foam, which is dissolved in methylene chloride containing 4% methanol and 0.2% ammonia chromatographed on 250 g silicagel with this solution. Fractions obtained
- 1st 1.3 g less unpolar substances (thrown away)
2nd 900 mg Fraction: uniform on t.l.c.
3rd 700 mg Fraction: mixture
4th 1.95 g Fraction 3: uniform on t.l.c.

The more polar fraction (4) contains the title compound which is crystallized twice from ethyl acetate/hexane. M.pt. 173-175°C.

In analogous manner the following compounds of formula I are obtained:-

The compounds of the invention exhibit pharmacological activity and are therefore useful as pharmaceuticals, e.g. for therapy.

In particular the compounds exhibit serotonin M receptor antagonist activity as indicated in standard tests. For example, in one test the action of the compounds in inhibiting the action of serotonin in reducing the amplitude of the compound action potential from the isolated rabbit vagus nerve was observed according to the principles of Riccioppo Neto, *European Journal of Pharmacology* (1978) 49 351-356, under conditions permitting differentiation between action potentials generated in myelinated nerve fibres (A fibres) and those generated in small non-myelinated fibres (C fibres) as described by B. Oakley and R. Schater, *Experimental Neurobiology, A Laboratory Manual*, University of Michigan Press, 1978, p85 to 96. Serotonin itself exerts its effect selectively on the C-fibres progressively with dosage. This action of serotonin is not blocked by the known serotonin antagonists, metitepine, methysergide, BOL - 148, which have been said to block D receptors for serotonin, but not M receptors (see Gaddam and Picarilli, *Brit. J. Pharmacol.* (1957), 12 323-328). It therefore appears that serotonin reduces the amplitude of the action potential carried by the C fibres through an effect mediated by M receptors for serotonin which are located on these nerve fibres.

The test may be effected by establishing a dose response curve for serotonin (10^{-7} - 5×10^{-6} M) after setting up the nerve. The serotonin is washed out and when the C fibre action potential has regained its original amplitude the compound of the invention at a set concentration of from about 10^{-10} M to about 10^{-6} M is preincubated with the nerve for 30 to 60 minutes. Varying concentrations of serotonin (10^{-7} to 10^{-4} M) are then applied with the compound of the invention at the concentration as was present during the preincubation period.

The M receptor antagonists of the invention either entirely block the action of serotonin (non-competitive antagonist) or cause a parallel shift of the serotonin/dose response curve to the right (i.e. increased concentrations of serotonin were required for effect) (competitive antagonist). The pD'_2 or pA_2 value may be obtained in the conventional manner.

The serotonin M receptor antagonist activity is also indicated by inhibiting the effect of serotonin on the isolated rabbit heart according to the method of J. R. Fozard and A. T. Mobarak Ali, *European Journal of Pharmacology*, (1978), 49, 109-112 at concentrations of 10^{-11} to 10^{-5} M of the compound of the invention. pD'_2 or pA_2 values may be calculated in the conventional manner.

The action of the compounds as serotonin M receptor antagonists for the treatment of analgesia is confirmed by action in the hot plate test at a dose of from about 0.1 to 100 mg/kg s.c. or p.o.

The serotonin M receptor antagonist activity is furthermore indicated in the cantharidine blister base test at a concentration of about 10^{-8} M. A blister is produced on the skin of the forearm of human volunteers with cantharidine. When serotonin is applied to the base of such blisters it produces pain which can be measured, the intensity being proportional to the concentration of serotonin applied. The procedure has been described by C. A. Keele and D. Armstrong in *Substances producing Pain and Itch*, Edward Arnold, London, 1964, p. 30 to 57. This algic action of serotonin is not inhibited by the serotonin D receptor antagonists such as lysergic acid diethylamide or its bromo derivative and is therefore believed to be mediated by M receptors.

In the procedure followed the area under the curve instead of the peak amplitude is measured by a linear integrator coupled to a pain intensity indicator which is operated by the volunteer. With increasing concentrations of serotonin a cumulative dose-response curve to serotonin may be obtained. When no further response on increasing the serotonin concentration is obtained, the serotonin is washed off and the blister incubated with physiological buffer solution for at least 40 minutes before the compound of the invention is applied. The test substance is preincubated with the blister base for 30 minutes at a concentration of about 10^{-8} M before varying concentrations of serotonin are applied. A pA_2 value may be obtained in the conventional manner.

The compounds of the invention are therefore be indicated for use as serotonin M receptors antagonists e.g. for the treatment of pain, especially migraine, vascular and cluster headaches and trigeminal neuralgia and also for the treatment of heart circulation disorders, e.g. for the treatment of sudden death, and as anti-psychotics.

An indicated daily dose is from about 0.5 to 500 mg conveniently administered in divided doses in unit dosage form 2 to 4 times a day containing from about 0.2 to about 250 mg of the compound or in sustained release form.

The compounds of the invention furthermore exhibit anti-arrhythmic activity as indicated by their serotonin M receptor antagonist activity and also in standard tests. For example the compounds inhibit arrhythmias induced by norepinephrine in anaesthetized rats. In this test infusions of norepinephrine (3 to 10 microgram/animal body weight) are given until an arrhythmic phase as indicated by ECG measurements lasts longer than 10 seconds duration. After control of 3 consecutive injections of norepinephrine the compound of the invention is injected at from about 10 to about 500 microgram/kg animal body weight followed by norepinephrine injections. The arrhythmic phase is reduced, or abolished depending on the dose of test compound.

The compounds are therefore indicated for use as anti-arrhythmic agents. As indicated daily dose is from about 0.5 to about 500 mg conveniently administered orally or by injection in divided doses 2 to 4 times a day or in unit dosage form containing from about 0.2 to about 250 mg, or in sustained release form.

The present invention accordingly provides a compound of the invention in pharmaceutically acceptable form, e.g. in free base form, or pharmaceutically acceptable acid addition salt form or quaternary

ammonium salt form, for use as a pharmaceutical, particularly for use as a serotonin M antagonist for those diseases where blockage of serotonin M receptors would be expected to have beneficial effects, e.g. as an analgesic agent, especially as an anti-migraine agent and as an anti-arrhythmic agent.

The preferred indication is the analgesic indication. The preferred compounds are the title compounds of Examples 1 and 2.

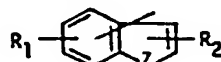
The compounds of the invention may be administered in free base form, or in pharmaceutically acceptable salt form, e.g. suitable acid addition salts and quaternary ammonium salts. Such salts exhibit the same order of activity as the free bases. The present invention accordingly also provides a pharmaceutical composition comprising a compound of the invention, in free base form or an acid addition salt thereof or a quaternary ammonium salt thereof, in association with a pharmaceutical carrier or diluent. Such compositions may be formulated in conventional manner so as to be for example a solution or a tablet.

CLAIMS

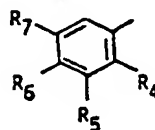
1. A process for the production of a compound of formula I

A-B-C-D-

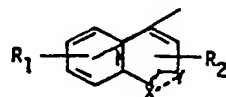
wherein A is a group of formula



(a)

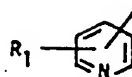


(b)



(c)

oder



(d)

wherein the free valence is attached to either fused ring in formula (a) or (c),

X-Y is $-\text{CH}=\text{CH}-$, $-\text{O}-\text{CH}_2-$ or $-\text{N}=\text{CH}-$,

Z is $-\text{CH}_2-$, $-\text{NR}_3-$, $-\text{O}-$, or $-\text{S}-$,

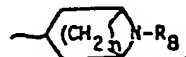
R₁ and R₂ are independently hydrogen, halogen, (C₁₋₄)-alkyl, (C₁₋₄)-alkoxy, hydroxy, amino, (C₁₋₄)-alkylamino, di(C₁₋₄)-alkylamino, mercapto or (C₁₋₄)-alkylthio, R₃ is hydrogen (C₁₋₄)-alkyl, (C₃₋₅)-alkenyl, aryl or arylalkyl,

R₄ to R₇ are independently hydrogen, amino, nitro, (C₁₋₄)-alkylamino, di(C₁₋₄)-alkylamino, halogen, (C₁₋₄)-alkoxy, (C₁₋₄)-alkyl, (C₁₋₄)-alkanoylamino, pyrrolyl, sulfamoyl, or carbamoyl

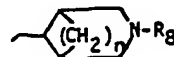
B is $-\text{CO}-$ or $-\text{SO}_2-$

C is $-\text{O}-$ or $-\text{NH}-$

D is a group of formula



(e)



(f)



(g)

oder



(h)

- wherein R_8 is hydrogen, (C_{1-7}) alkyl, (C_{3-5}) alkenyl or aralkyl and n is 2, 3 or 4 with the provisos that
- 1) when A is a group of formula (a) and B is $-\text{CO}-$, then D is other than a group of formula (e) or (g),
 - 2) when A is a group of formula (b) wherein R_4 to R_7 are each hydrogen, B is $-\text{CO}-$ and C is $-\text{O}-$, then D is other than a group of formula (f), wherein R_8 is methyl, or (h) wherein R_8 is methyl,
 - 5 3) when A is a group of formula (d) wherein R_1 is hydrogen or alkoxy and B is $-\text{CO}-$ then D is other than a group of formula (e) wherein n is 2,
 - 4) when A is a group of formula (d) wherein R_1 is hydrogen, B is CO and C is $-\text{O}-$ then D is other than a group of formula (g);
 - 5) when A is a group of formula (b), B is $-\text{CO}-$ and D is (e) or (g) then at least one of R_4 to R_7 in the formula
 - 10 (b) is sulfamoyl or carbamoyl,
 - their acid addition salts and quaternary ammonium salts, which includes the step of
 - a) condensing an appropriate compound of formula II

A-B-OH

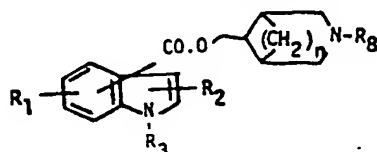
II

- 15 wherein A and B are as defined above, a reactive derivative thereof, or a precursor of the acid or derivative, with an appropriate compound of formula III

20 H-C-D

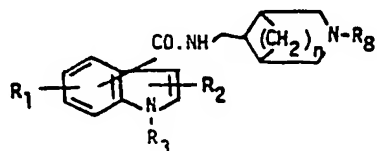
III

- wherein C and D are as defined above, or a precursor of the compound or,
- b) alkylating a compound of formula I having a secondary amino group to produce a compound of formula I with a tertiary amino group,
 - 25 c) deprotecting any protected form of a compound of formula I to obtain a compound of formula I,
 - d) halogenating a compound of formula I wherein A is a group of formula (a) and R_2 is hydrogen to obtain the corresponding compound wherein R_2 is halogen, or
 - e) alkoxyating a compound of formula I wherein A is a group of formula (a) and R_2 is halogen to obtain the corresponding compound wherein R_2 is alkoxy, and
 - 30 recovering the resultant compound of formula I as such or as an acid addition salt or as a quaternary ammonium salt thereof.
 2. A process for the production of a compound of formula I or an acid addition salt or quaternary acid addition salt thereof, substantially as hereinbefore described with reference to any one of the examples.
 3. A compound of formula I or an acid addition salt or a quaternary ammonium salt thereof whenever
 - 35 produced by a process of claim 1 or 2.
 4. A compound of formula I or an acid addition salt or a quaternary ammonium salt thereof.
 5. A compound of claim 4 wherein
 - A is a group of formula (c) or (d)
 - B is CO and
 - 40 D is a group of formula (e) or (g)
 - or an acid addition salt or a quaternary ammonium salt thereof.
 6. A compound of claim 4 wherein
 - A is a group of formula (a), or a group of formula (b) wherein each of R_4 to R_7 is other sulfamoyl or carbamoyl
 - 45 B is CO, and
 - D is a group of formula (f) or
 - an acid addition salt or as a quaternary ammonium salt thereof.
 7. A compound of claim 6 wherein R_1 and R_2 are each other than alkyl or an acid addition salt or as a quaternary ammonium salt thereof.
 - 50 8. A compound of claim 4 having the formula Ia



Ia

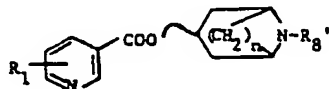
- 55 wherein the carbonyl group is attached to either fused ring, and R_1 , R_2 , R_3 , R_8 and n are as defined in claim 1, as well as acid addition salts and quaternary ammonium salts thereof.
- 60 9. A compound of claim 4 having the formula Ib



Ib

wherein the carbonyl group is attached to either fused ring, R_1 , R_2 , R_3 , R_8 and n are as defined above, as well as acid addition salts and quaternary ammonium salts thereof.

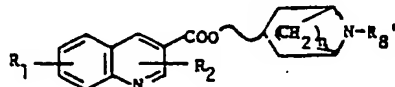
10. A compound of claim 4 having the formula Ic



Ic

wherein R_1 and n are as defined above and R_8' is hydrogen or (C_{1-4}) alkyl, and subject to the provisos to formula I in claim 1 as well as acid addition salts and quaternary ammonium salts and quaternary ammonium thereof.

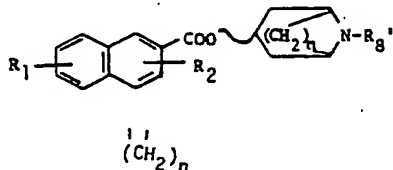
11. A compound of claim 4 having the formula Id



Id

wherein R_1 , R_2 , n and R_8' are as defined in claims 1 and 10, as well as acid addition salts thereof.

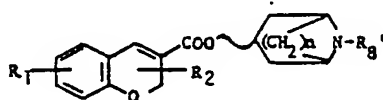
12. A compound of claim 4 having the formula Ie



Ie

wherein R_1 , R_2 , n and R_8' are as defined in claims 1 and 10 as well as acid addition salts and quaternary ammonium salts thereof.

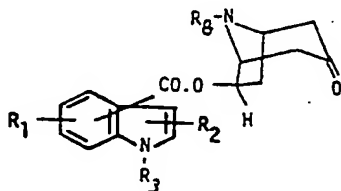
13. A compound of claim 4 having formula If



If

wherein R_1 , R_2 , n and R_8' are as defined in claims 1 and 10, as well as acid addition salts and quaternary ammonium salts thereof.

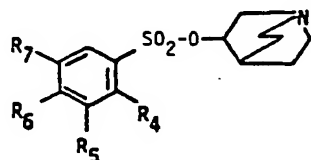
14. A compound of claim 4 having the formula Ig



Ig

wherein the carbonyl group may be attached to either fused ring, R_1 , R_2 , R_3 , R_8 and n are as defined in claim 1, as well as acid addition salts and quaternary ammonium salts thereof.

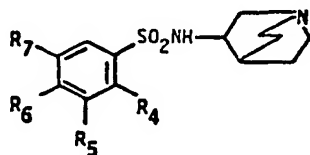
15. A compound of claim 4 having the formula Ih



I h

wherein R_4 to R_7 are as defined in claim 1, as well as acid addition salts and quaternary ammonium salts thereof.

16. A compound of claim 4 having the formula II



II

wherein R_4 to R_7 are as defined in claim 1, as well as acid addition salts and quaternary ammonium salts thereof.

17. A compound of claim 4 which is indol-3-yl carboxylic acid 9-anti-3-methyl-3-azabicyclo[3.3.1]non-9-yl amide or an acid addition salt or a quaternary ammonium salt thereof.

18. A compound of claim 4 wherein A is (a), R_1 is H, R_2 is H, Z is NH, B is CO, ring position of B is (3), C is O, D is (f), Configuration is anti, n is 3, R_8 is CH_3 or an acid addition salt or a quaternary ammonium salt thereof.

19. A compound of claim 4 wherein A is (a), R_1 is H, R_2 is H, Z is NH, B is CO, ring position of B is (3), C is O, D is (f), Configuration is syn, n is 3, R_8 is CH_3 or an acid addition salt or a quaternary ammonium salt thereof.

20. A compound of claim 4 wherein A is (c), R_1 is H, R_2 is H, X-Y is $-N=CH-$, B is CO, position of B is (3), C is O, D is (e), Configuration is endo, n is 3, R_8 is CH_3 or an acid addition salt or a quaternary ammonium salt thereof.

21. A compound of claim 4 wherein A is (d), R_1 is H, B is CO, ring position of B is (3), C is O, D is (e), Configuration is endo, n is 3, R_8 is CH_3 or an acid addition salt or a quaternary ammonium salt thereof.

22. A compound of claim 4 wherein A is (c), R_1 is H, R_2 is H, X-Y is $CH=CH$, B is CO, ring position of B is (2), C is O, D is (e), Configuration is endo, n is 3, R_8 is CH_3 or an acid addition salt or a quaternary ammonium salt thereof.

23. A compound of claim 4 wherein A is (c), R_1 is H, R_2 is H, X-Y is $O-CH_2$, B is CO, ring position of B is (3), C is O, D is (e), Configuration is endo, n is 3, R_8 is CH_3 or an acid addition salt or a quaternary ammonium salt thereof.

24. A compound of claim 4 wherein A is (a), R_1 is H, R_2 is H, Z is NH, B is CO, ring position of B is 3, C is O, D is (h), Configuration of h is (1S*,5R*,6R*) or an acid addition salt or a quaternary ammonium salt thereof.

25. A compound of claim 4 wherein A is (b), R_4 is H, R_5 is H, R_6 is CH_3 , R_7 is H, B is SO_2 , C is O, D is (g), ring position of (g) is 3 or an acid addition salt or a quaternary ammonium salt thereof.

26. A compound of claim 4 wherein A is (b), R_4 is H, R_5 is H, R_6 is CH_3 , R_7 is H, B is SO_2 , C is NH, D is (g), ring position of (g) is 3 or an acid addition salt or a quaternary ammonium salt thereof.

27. A compound of claim 4 wherein A is (b), R_4 is H, R_5 is $CONH_2$, R_6 is H, R_7 is H, B is CO, C is NH, D is (g), ring position of (g) is 3 or an acid addition salt or a quaternary ammonium salt thereof.

28. A compound of claim 4 wherein A is (b), R_4 is OCH_3 , R_5 is H, R_6 is H, R_7 is SO_2NH_2 , B is CO, C is NH, D is (g), ring position of (g) is 3 or an acid addition salt or a quaternary ammonium salt thereof.

29. A compound of claim 4 wherein A is (B), R_4 is H, R_5 is H, R_6 is H, R_7 is SO_2NH_2 , B is CO, C is NH, D is (g), ring position of (g) is 3 or an acid addition salt or a quaternary ammonium salt thereof.

30. A compound of any one of claims 3 to 29 or a pharmaceutically acceptable acid addition salt or quaternary ammonium salt for use as a pharmaceutical.

31. A compound of any one of claims 3 to 29 or a pharmaceutically acceptable acid addition salt or quaternary ammonium salt thereof for use as a serotonin M antagonist, an analgesic agent, an anti-migraine agent or an anti-arrhythmic agent.

32. A pharmaceutical composition comprising a compound of any one of claims 3 to 29 or a pharmaceutically acceptable acid addition salt or quaternary ammonium salt thereof in association with a pharmaceutical carrier or diluent.

33. A compound of formula III as defined in claim 1 wherein C is NH and D is a group of formula f.